PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: J. Timothy GREENAMYRE, et al
Serial No.: 09/148,973 Group No.: 1627
Filed: September 4, 1998 Examiner.: Maurice Garcia Baker
For: METHODS OF ADMINISTERING AN AMPA RECEPTOR ANTAGONIST TO TREAT DYSKINESIAS ASSOCIATED WITH DOPAMINE AGONIST THERAPY

Attorney Docket No.: U 946765-7

Commissioner for Patents
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DECLARATION UNDER 37 CFR 1.132

I, Frank S. Menniti, PhD, hereby declare:

1. My technical background and experience are as described in my curriculum vitae which is annexed hereto as Exhibit 1. I submit this declaration in connection with the prosecution of the above US patent application ("the application"). I am a co-inventor of the subject matter described and claimed in the application and am fully familiar with its contents.

2. The application describes and claims a method of treating dyskinesia associated with dopamine agonist therapy in a mammal which comprises administering to the mammal an amount of an AMPA receptor antagonist that is effective in treating such dyskinesia. A person of ordinary skill in the art at the time of filing the application, September 4, 1998, would have been a neurologist or a person with a degree in neurology. Such person of ordinary skill in the art would have been familiar with the references cited below, which are also listed in Exhibit 2, annexed hereto.

3. As of the application filing date, it was known that the use of therapies that directly stimulate dopamine receptors such as the chronic administration of dopamine agonist therapy in the treatment of Parkinson's disease, could provoke motor abnormalities, including choreatic dyskinesias and dystonias (see the application at page 1, lines 18-25). I understand that an issue has arisen in the prosecution of the application as to whether the disclosure in Arnold et al US Patent 5,670,516 ("Arnold et al") would have provided one of skill in the art with a reasonable expectation of success in the treatment of such dopamine agonist-induced dyskinesias by the administration of an AMPA receptor antagonist. To address this issue, it is first necessary to determine what one of skill in the art would have understood from the Arnold et al disclosure.

4. Arnold et al teach that blocking AMPA receptors is an effective way to treat certain neurological disorders, including but not limited to drug-induced Parkinson's Disease and tardive dyskinesia (Arnold et al at column 1, line 55 to column 2, line 9). Arnold et al do not, however, disclose that the blocking of AMPA receptors would be an effective way to treat all neurological disorders, regardless of etiology, and they specifically do not disclose that the blocking of AMPA receptors would be an effective way to treat a dyskinesia associated with dopamine agonist therapy. The question then is whether the teaching in Arnold et al that one can treat certain neurological disorders, such as tardive dyskinesia, by blocking AMPA receptors would provide one of skill in the art with an expectation that one can treat dopamine agonist-induced dyskinesias in the same way. In answering this question, it is important to understand that when neurological disorders, such as tardive dyskinesia,

are classified by their etiology, the fact that different disorders fall within the same classification (e.g., "dyskinesia") does not mean that they can be successfully treated with the same therapy, as next discussed.

5. Tardive dyskinesia (TD) is one in a broad category of movement disorders thought to involve pathology of the basal ganglia, which category also includes Parkinson's disease, drug-induced parkinsonism, the choreas, ballism, the athetoses, the dystonias including tardive (and other) dystonias, akathisia, Huntington's disease, and several degenerative and atrophic syndromes, (see US Patent 5,670,539 at column 5, line 61-column 6, line 7). As of the filing date of the application, it was poorly understood how basal ganglia control movements, and it was thought that the manifestation of abnormal movement disorders, such as TD, at a minimum involved several neurotransmitter systems, and that vulnerability to such disorders might be multifaceted (US Patent 5,670,539 at column 7, lines 3-7). Significantly one facet of this vulnerability was thought to involve an imbalance in serotonin-dopamine interactions in the brain (US Patent 5,670,539 at column 8, line 60-column 9, line 5).

6. In view of the diverse and multifaceted nature of the movement disorders and the apparent involvement of a number of different neurotransmitter systems, including neurotransmitter system(s) involving dopamine, one of skill in the art could not have predicted that a dyskinesia associated with a dopamine **agonist** therapy could be effectively treated in the same manner as a dyskinesia associated with a dopamine **antagonistic** therapy. In particular, one of skill in the art could not have known what

effects administering an AMPA receptor antagonist could have on the seratonin-dopamine interactions in patients treated with L-dopa and whether such effects would, for example, offset or exacerbate the effects caused by the dopamine agonist therapy.

7. Indeed, data in the literature at the time of our application and Arnold et al indicated that an AMPA receptor antagonist would potentiate dopamine agonist-induced dyskinesias. Specifically, Klogether et al (Klockgether et al., 1991) and Loschmann et al (Loschmann et al., 1991) demonstrated that an AMPA receptor antagonist potentiates the effects of a dopamine agonist in animal models of bradykinesia, one of the neurological symptoms of Parkinson's disease. This data suggests that AMPA receptor antagonists and dopamine agonists act synergistically in producing behavioral responses. We found, instead, that in the case of dopamine agonist-induced dyskinesias, AMPA receptor antagonists oppose the effect of dopamine agonists. Thus, our claim that an AMPA antagonist inhibits dopamine agonist-induced dyskinesias was unanticipated and contraindicated at the time of publication of Arnold et al.

8. I understand that an issue has also arisen as to whether the disclosure in Papa and Chase, Annals of Neurology, 39(5), pp. 574-578 (referred to by the Examiner as Stella et al) would have provided one of skill in the art with a reasonable expectation of success in the use of AMPA receptors to treat dopamine agonist-induced dyskinesias since these authors teach that an NMDA receptor antagonist can reduce L-DOPA-induced dyskinesias and since AMPA and NMDA receptors are subtypes of the same

receptor. However, while it is true that AMPA and NMDA receptors are both ionotropic glutamate receptors, it is well known that these two receptors have clearly distinct physiologies (Seeburg, 1993; Dingledine et al., 1999). Consistent with this fact are the numerous reports in the literature that AMPA and NMDA receptor antagonists have very different physiological effects (Browne and McCulloch, 1994; Durmuller et al., 1994; Sheardown et al., 1993; Papa et al., 1993). Thus, the observation by Papa and Chase that an NMDA receptor antagonist reduced dopamine agonist-induced dyskinesias would not have led to the deduction of the utility of an AMPA receptor antagonist to treat dopamine agonist-induced dyskinesias. AMPA and NMDA receptors serve distinct physiological functions and antagonists for the two receptor classes have distinct physiological effects. In fact, in light of the papers by Klockgether et al and Loschmann et al, the use of an AMPA receptor antagonist to treat dopamine agonist-induced dyskinesias was contraindicated prior to the application.

9. In view of the above, it is my belief that there is no disclosure in the prior art, including the Arnold et al patent and the Papa and Chase article, from which one of skill in the art could have expected that blocking AMPA receptors would be an effective way to treat a dyskinesia associated with dopamine agonist therapy.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity or the application of any patent issued thereon.

Date: 2-6-2004

Frank S. Menniti, PhD

EXHIBIT 1

CURRICULUM VITAE

Name: Frank S. Menniti, Ph.D.

Date & Place of Birth: May 10, 1956; Sewickley, PA

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Current Home Address: 10 Reynolds Hill Road
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Current Work Address: Pfizer Global Research and Development
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Education:

09/83 - 12/87 Ph.D., Pharmacology, University of North Carolina, Chapel Hill, North Carolina

09/78 - 09/81 M.S., Neuroendocrinology, Massachusetts Institute of Technology, Cambridge, Massachusetts

09/74 - 06/78 B.A., Psychology, Franklin and Marshall College, Lancaster, Pennsylvania

Brief Chronology of Research Experience:

04/92 - Date Principal Research Investigator, Pfizer Global Research and Development. Principal investigator in development of therapies for the treatment of neurodegenerative and psychiatric diseases.

01/88-04/92 Senior Staff Fellow, National Institute of Environmental Health Sciences. Principal investigator in studies of receptor regulation and signal transduction through the inositol phosphate/intracellular calcium signaling cascade.

04/82 - 01/88 Research Biochemist, Wellcome Research Laboratories and graduate student, University of North Carolina. Principal investigator in studies of catecholamine biosynthesis and the role of ascorbic acid in bovine adrenomedullary chromaffin cells.

09/81 - 04/82 Research Assistant II, Harvard Medical School. Conducted biochemical and behavioral studies on peptide hormonal regulation of maternal behavior in the rat.

09/78 - 09/81 Graduate student, Massachusetts Institute of Technology. Principal investigator in biochemical and behavioral studies into the interaction of steroid hormones and neurotransmitters in the rat central nervous system.

09/77 - 06/78 Undergraduate student, Franklin and Marshall College. Independent study into the role of olfaction and spatial cues in maze performance and into the psychopharmacology of exploratory behavior in rodents.

06/77 - 08/77 Participant in the National Science Foundation Undergraduate Research Program, Brown University. Participated in studies of observing responses and eye movement during choice behavior in the stumptail macaque.

Awards and Honors:

06/78	Phi Beta Kappa
10/77	Psi Chi, Psychology Honor Society

Affiliations:

Sigma Xi, Scientific Research Society
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ABSTRACTS AND PRESENTATIONS

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